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Body sodium-blood volume state, aldosterone, and cardiovascular responsiveness after calcium entry blockade with nifedipine

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Body sodium-blood volume state, aldosterone, and cardiovascular responsiveness after calcium entry blockade with nifedipine. Exchangeable sodium, blood volume, plasma norepinephrine (NE), epinephrine, renin and aldosterone levels, and pressor responses to infused NE or angiotensin II (AII) were assessed in ten patients with essential hypertension on placebo, following 6 to 8 weeks of calcium-antagonist nifedipine (NIF), 3 × 10 to 20 mg/day, and after 6 to 8 weeks on NIF combined with the diuretic chlorthalidone (CHLOR), 25 to 50 mg/day. Pressor effects of infused calcium also were evaluated on placebo and NIF. Supine blood pressure was decreased from 151/97 ± 5/2 (SEM) to 132/88 ± 6/2 mm Hg after NIF alone ($P < 0.05$) and to 124/83 ± 7/3 mm Hg after NIF + CHLOR ($P < 0.01$). Body wt was increased from 72.7 to 73.9 kg on NIF alone ($P < 0.05$), but decreased to 72.1 ($P < 0.05$ compared with placebo) after adding CHLOR. Exchangeable sodium also rose from 2642 ± 237 to 3360 ± 266 mmoles on NIF (+ 27%; $P < 0.01$) and returned to control values (2638 ± 248 mmoles) after addition of CHLOR. Plasma volume was only slightly modified on NIF (from 2621 ± 193 to 2751 ± 160 ml; + 5%), but was reduced to 2232 ± 231 ml on NIF + CHLOR ($P < 0.05$). Responses of circulating aldosterone to AII were similarly diminished ($P < 0.01$) during both conditions. Heart rate, supine and upright plasma renin, aldosterone and catecholamine levels, and pressor responses to NE, AII, or calcium were not consistently changed. These findings indicate that in the established phase of treatment, NIF may exert its antihypertensive effect without necessarily altering cardiovascular responsiveness to NE and AII. However, calcium antagonism with NIF blunts aldosterone responsiveness to AII and this alteration persists following addition of a diuretic. Mild sodium retention may develop on NIF, and much of this sodium seems to be distributed to an extracellular compartment. The addition of a thiazide diuretic may restore body sodium, slightly reduce blood volume, and complement the blood pressure-lowering effect of calcium antagonist therapy with NIF in essential hypertension. Furthermore, the pressor responses to acute mild hypercalcemia are not mediated by an enhanced influx of calcium through the slow transmembranous channels.

Sodium corporel-volume sanguin, aldostérone, et réponse cardiovasculaire après blocage de l'entrée du calcium par la nifédipine. Le sodium échangeable, le volume sanguin, la noradrénaline (NE), l'adrénaline, la rénine, et l'aldostérone plasmatiques, et les réponses pressives à une perfusion de NE ou d'angiotensine II (AII) ont été mesurés chez dix malades atteints d'hypertension essentielle sous placebo, après 6 à 8 semaines de nifédipine (NIF) un antagoniste du calcium, 3 × 10 à 20 mg/jour, et après 6 à 8 semaines de NIF en association avec de la chlorthalidone (CHLOR) un diurétique, 25 à 50 mg/jour. Les effets presseurs d'une perfusion de calcium ont également été évalués sous placebo et sous NIF. La pression sanguine en décubitus était diminuée de 151/97 ± 5/2 (SEM) à 132/88 ± 6/2 mm Hg après NIF seul ($P < 0.05$) et à 124/83 ± 7/3 mm Hg après NIF + CHLOR ($P < 0.01$). Le poids corporel a augmenté de 72.7 à 73.9 kg avec NIF seul ($P < 0.05$), mais a diminué à 72.1 ($P < 0.05$ par rapport au placebo) après addition de CHLOR. Le sodium échangeable a également augmenté de 2.642 ± 237 à 3.360 ± 266 mmoles avec NIF (+ 27%; $P < 0.01$) et est revenu aux valeurs contrôles (2.638 ± 248 mmoles) après addition de CHLOR. Le volume plasmatique n'était que modifié légèrement avec NIF (de 2.621 ± 193 à 2.751 ± 160 ml; + 5%), mais était réduit à 2.232 ± 231 ml avec NIF et CHLOR ($P < 0.05$). Les réponses de l'aldostérone circulante à AII étaient également diminuées ($P < 0.01$) dans chaque condition. Le rythme cardiaque, la rénine plasmatique couchée et debout, les niveaux d'aldostérone et de catécholamines, et les réponses pressives à NE, AII ou calcium n'étaient pas changés de façon consistante. Ces résultats indiquent qu'à la phase établie du traitement, NIF pourrait exercer son effet hypotenseur sans altérer nécessairement les réponses cardiovasculaires à NE et AII. Cependant l'antagonisme calcique avec NE diminue la réponse de l'aldostérone à AII, et cette altération persiste après adjonction d'un diurétique. Une rétention sodée modérée peut apparaître sous NIF, et la plupart de ce sodium semble être distribué dans le compartiment extra-cellulaire. L'adjonction d'un diurétique thiazidique pourrait restaurer le sodium corporel, diminuer légèrement le volume sanguin, et compléter l'effet d'abaissement de la pression sanguine du traitement par l'antagoniste calcique avec NIF dans l'hypertension essentielle. De plus, les réponses pressives à une hypercalcémie aiguë modérée ne sont pas médiées par un influx augmenté de calcium à travers les canaux transmembranaires lents.

The potential of transmembranous calcium entry blockers, given either as single dose or at short term, to reduce blood pressure (BP) in essential and certain other forms of hypertension is now well established [1–4]. A decrease in basal vascular muscle tone, resulting from reduced intracellular free calcium, is probably of prime importance for this action. Moreover, calcium antagonists may modulate BP through additional regulatory factors, such as the sympathetic and renin-angiotensin systems [1, 5, 6], the vascular reactivity to norepinephrine (NE) or angiotensin II (AII) [7–10], and perhaps also the body sodium-fluid volume state. In fact, the addition of thiazide-

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typediuretics to calcium antagonists can enhance the antihypertensive effect [11, 12].

Some calcium antagonists may acutely promote renal sodium excretion [13–17], but no data on body sodium during such treatment, alone or in combination with diuretics, are available. Observations on cardiovascular pressor responsiveness in humans receiving calcium antagonists are scant and partly inconsistent [7–10]. Yet another aspect deserving clarification is the question whether and to what extent calcium antagonists may block the pressor influence [18, 19] of an increase in serum calcium. The present study was designed to address these three problems. The body sodium-blood volume state, pressor responsiveness to NE, AII, or calcium as related to concomitant plasma NE, AII, and calcium concentrations, as well as the responsiveness of plasma aldosterone to AII, were evaluated in patients with benign essential hypertension under placebo conditions and following 6 to 8 weeks of treatment with the calcium antagonist nifedipine alone or in combination with the diuretic chlorthalidone.

Methods

Subjects

Ten patients (6 women and 4 men) with mild essential hypertension, aged 44 to 69 yrs [mean 56.7 ± 2.5 (± SEM) yrs] were studied. Arterial hypertension was defined by repeated BP measurements > 140/90 mm Hg during a 3-month observation period. Secondary forms of hypertension were excluded by the usual tests. None of the patients showed clinical or laboratory evidence of congestive heart failure, cardiac arrhythmia, edema or renal failure (as defined by a serum creatinine ≧ 130 μmole/liter). Six patients were untreated; in the other four, all antihypertensive drugs and potassium supplements were discontinued at least 4 weeks before study. The patients, who had given their informed consent to the study, were instructed to ingest a normal diet, but without salty foods or adding salt to their food [20].

Patients were started on placebo, one capsule t.i.d. for 4 weeks. The placebo capsules were then replaced by the calcium antagonist nifedipine, 10 mg t.i.d. This dose was increased to 20 mg t.i.d. in two patients in whom BP was still ≧ 165/100 mm Hg after 2 weeks of treatment. The mean dose from the third week on was 36 ± 3 (± SEM) mg/day. Dosing of nifedipine t.i.d. has been found adequate to provide a sustained drug effect, particularly after 6 weeks of administration [21].

After 6 to 8 weeks nifedipine monotherapy, the diuretic chlorthalidone, 25 to 50 mg/day [mean dose 34 ± 3 (± SEM) mg/day], was added to nifedipine during an additional 6- to 8-week period. The study was conducted single-blind. At the end of each period (placebo phase, nifedipine, nifedipine + chlorthalidone), the following studies (A, B, and C) were performed, after overnight fast on three different mornings within 4 to 6 days.

Study A

Sixty μCi of ^{24}Na were administered and 24-hr urine was collected for determination of ^{24}Na [22], sodium, potassium, calcium, phosphate, NE and epinephrine excretion rates. At the end of this collection period, BP and heart rate were measured and blood was drawn for counting of ^{24}Na and for determination of plasma sodium, potassium, calcium, phosphate, creatinine, renin activity (PRA), aldosterone, NE and epinephrine levels, and serum protein concentration. These blood samples were obtained after 1 hr of recumbency between 8 and 9 A.M. through an indwelling intravenous cannula inserted 60 min previously. For measurement of plasma and blood volumes [22, 23], 2.5 μCi of ^{125}I-RIHSA were then injected intravenously through an intravenous cannula on the contralateral arm, and blood for determination of whole blood and plasma ^{125}I concentrations was drawn from the ipsilateral cannula 10 min later. BP, heart rate, PRA, aldosterone, NE and epinephrine levels were measured again after 1 hr of ambulation, according to our standard procedure [20].

Study B

One to 3 days later, an infusion of NE or AII was performed in the supine position as described previously [24, 25]. A dose of the drug was taken 1 hr before the infusion.

Following a 60-min equilibration period with slow intravenous infusion of 5% dextrose (6 ml/hr by constant infusion pump), basal BP and heart rate were obtained and blood samples were drawn from the arm contralateral to the infusion through an indwelling intravenous cannula (inserted 45 to 60 min previously) for determination of basal PRA, NE and epinephrine levels. These blood samples were collected between 8:30 and 9:30 A.M. The dextrose solution was then replaced by a solution of NE (1-norepinephrine-bitartrate) in 5% dextrose, which was infused continuously at step-wise increasing dose rates of 20, 40 and 100 ng/kg/min; in four of the patients a further dose of 200 ng/kg/min had to be given to achieve the target increase in mean BP (20 mm Hg). Each dose was infused during 20 min. BP and heart rate were measured every min during the last 10 min of each infusion step; at the end of each infusion period, blood was collected from the arm contralateral to the infusion for determination of plasma NE. The NE infusion was replaced by 5% dextrose, which was infused during 45 to 60 min at constant rate. After this second equilibration period, basal blood pressure, heart rate, PRA, AII and aldosterone levels were determined; the dextrose infusion was then replaced by a solution of AII (Hypertensin, Ciba, Basel, Switzerland) in 5% dextrose, which was infused continuously at increasing dose rates of 2, 4 and 10 ng/kg/min. In three of the patients, a further dose of 20 ng/kg/min had to be given to increase the diastolic BP by at least 20 mm Hg. Each dose was infused during 20 min. BP and heart rate were recorded as described previously. At the end of each AII infusion step, blood was drawn for determination of plasma AII and aldosterone.

Study C

One to three days later, the response of BP to an acute mild hypercalcemia was studied. Following an equilibration period of 60 min with intravenous infusion of 5% dextrose (6 ml/hr by constant infusion pump) in the supine position, basal BP and heart rate were obtained and blood drawn for determination of plasma calcium, PRA, NE and epinephrine concentrations. The dextrose solution was then replaced by a solution of calcium-gluconate, which was infused at a constant rate (0.034 mg calcium/kg/min) during 180 min [7]. BP and heart rate were recorded every hr, and blood was collected from the arm contralateral to the infusion for determination of plasma cal-

cium and, at 120 and 180 min, for determination of PRA, NE and epinephrine.

Analytical procedures

BP was measured using standard cuff and sphygmomanometer. Each pressure was a mean of three readings. Phase 5 was taken as diastolic BP; mean BP was calculated as the sum of the diastolic (disappearance of sounds) and one-third of the pulse pressure. During infusion studies, BP was measured with the automatic recorder Physiometrics SR II (Asulab, Neuchâtel, Switzerland). BP values recorded before and during infusion were the mean of 10 measurements. Sodium and potassium were determined by flame photometer, calcium and creatinine by autoanalyzer, proteins by Biuret and phosphate by Malachite green method [26]. Plasma and blood volume, or exchangeable sodium were measured by standard isotope dilution technique using ^{125}I human serum albumin and ^{24}Na, respectively [22, 23]. PRA, aldosterone, and AII were measured by radioimmunoassay [27–29], NE and epinephrine in plasma and urine by a radioenzymatic method [30], as reported previously from this laboratory [20, 24]. Cardiovascular responsiveness to NE, AII or calcium infusions was analyzed by blood level-BP response curves [7, 25].

Pressor doses of infused NE or AII required to increase the mean (NE-infusion) or diastolic (AII-infusion) BP by 20 mm Hg were calculated from the dose-BP response curves [7, 25]. Total plasma clearances of infused NE or AII were calculated by the ratio between the infused dose rate and the concomitant variations in plasma concentration [31, 32]. Since natural logarithmic transformation rather than absolute values followed a Gaussian distribution in this and many previous studies [20, 24, 25, 31], the natural logarithmic transformation of PRA, aldosterone, NE, epinephrine and pressor doses was used; statistical methods included paired and unpaired, two-tailed *t* test, and analysis of covariance [33].

Results

Study A

Compared to placebo conditions, nifedipine monotherapy after 6 to 8 weeks was associated with a significant ($P < 0.01$) decrease in supine BP and increases in mean body wt ($P < 0.05$) and total exchangeable sodium ($P < 0.01$) (Table 1). No consistent changes occurred in heart rate, hematocrit, plasma and blood volumes, plasma and urinary electrolytes, PRA, plasma aldosterone, plasma and urinary NE and epinephrine levels.

Combination treatment with nifedipine and chlorthalidone caused a further slight decrease in supine BP; upright BP also was significantly reduced as compared to placebo (Table 1). Exchangeable sodium was restored to the values observed under placebo conditions, while body wt, plasma, and blood volume were significantly lowered ($P < 0.05$ vs. placebo) and PRA was increased ($P < 0.05$). The other parameters were not consistently altered (Table 1).

Study B

Compared to placebo conditions, basal (pre-infusion) BP was lowered significantly ($P < 0.05$) after nifedipine monotherapy and decreased further on nifedipine-chlorthalidone combination treatment (Table 2). Basal (pre-infusion) plasma NE, AII, and aldosterone levels were not consistently modified by nifedipine monotherapy, but were increased slightly ($P < 0.05$) on nifedipine-chlorthalidone combination therapy (Table 2); basal epinephrine values were stable during the three periods (2.1 ± 0.4, 2.3 ± 0.5, and 2.1 ± 0.7 ng/dl).

Infusion rates of NE or AII correlated with concomitant increases in circulating NE or AII, respectively (Fig. 1). These relationships were similar under the three study conditions. Therefore, the plasma clearances of NE and AII during their infusions also were unaltered (Table 2).

Pressor responsiveness to NE, evaluated by pressor doses, the slope of infusion rate-BP response curves (Table 2), as well as plasma NE concentration-BP response curves (Fig. 2), was not consistently modified on nifedipine monotherapy or combination treatment. Moreover, the fall in heart rate in response to the pressor effect of NE infusion was also similar (Fig. 3). Pressor responsiveness to AII, evaluated by the same approach, also was unchanged (Table 2, Fig. 4).

Percentage increases in plasma aldosterone in response to stepwise increases in circulating AII were significantly ($P < 0.01$) blunted during nifedipine monotherapy or nifedipine-chlorthalidone combination treatment as compared to placebo (Fig. 5).

Study C

Calcium was infused during placebo and nifedipine monotherapy. Basal (pre-infusion) plasma calcium, PRA, NE, and epinephrine levels were similar during the two study conditions (Table 3). Calcium infusion significantly increased serum calcium (by about 0.3 mmole/liter, $P < 0.001$) and systolic BP ($P < 0.01$) (Fig. 6). The systolic pressor response to calcium was not decreased by nifedipine (+ 15 ± 4% vs. + 10 ± 3% on placebo), although pre-infusion BP was lower during nifedipine treatment.

Side effects

During nifedipine monotherapy, ankle or pretibial edema was noted in two patients, while palpitations, flush, or tendency for constipation were each reported by one subject. Leg edema disappeared during combination treatment, while the three other symptoms already tended to diminish during monotherapy phase.

Discussion

Monotherapy with nifedipine in our patients with mild essential hypertension reduced mean BP by 10% ($P < 0.01$), but mean body wt and exchangeable body sodium were significantly increased ($P < 0.05$ and $P < 0.01$, respectively) after 6 to 8 weeks of such treatment. The addition of the diuretic chlorthalidone induced a further decrease in blood pressure, removed the retained body sodium, and slightly but significantly lowered blood volume. This interaction with the sodium-fluid volume state may explain the enhanced antihypertensive efficacy when calcium antagonists are combined with diuretics [1, 11, 12].

A previous report described fluid volume retention during short- to long-term monotherapy with nifedipine [34]. The tendency for mild and sometimes transient leg edema on therapy with nifedipine or other calcium antagonists [35] is well known. On the other hand, renal sodium excretion is increased

Table 1. Clinical and biochemical features of patients with mild essential hypertension on placebo, after nifedipine alone, and after nifedipine-diuretic combination treatment

	Placebo	Nifedipine	Nifedipine + Chlorthalidone
Blood pressure, *mm Hg*			
supine	151/97 ± 5/2	132[a]/88[b] ± 6/2	124[b]/83[ce] ± 7/3
upright	142/97 ± 5/2	136/96 ± 5/3	125[ad]/93 ± 6/3
Pulse rate, *beats/min*			
supine	69 ± 3	67 ± 2	64 ± 2[ad]
upright	77 ± 2	79 ± 4	82 ± 3[a]
Body weight, *kg*	72.7 ± 3.9	73.9 ± 4.0[a]	72.1 ± 3.9[ae]
Hematocrit, *%*	41.7 ± 0.6	40.9 ± 3.2	41.9 ± 3.2
Exchangeable sodium, *mmoles*	2642 ± 237	3360 ± 266[b]	2638 ± 248[e]
% [g]	98 ± 6	123 ± 7[b]	97 ± 7[e]
Blood volume, *ml*	4210 ± 303	4279 ± 253	3969 ± 333[ae]
% [g]	99 ± 3	101 ± 3	96 ± 4[ad]
Plasma volume, *ml*	2621 ± 193	2751 ± 160	2232 ± 231[af]
% [g]	106 ± 6	110 ± 4	94 ± 7[ae]
Plasma sodium, *mmoles/liter*	141 ± 0.7	142 ± 0.8	139 ± 1.7
potassium, *mmoles/liter*	4.4 ± 0.1	4.5 ± 0.2	4.5 ± 0.4
calcium, *mmoles/liter*	2.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.1
phosphate, *mmoles/liter*	0.8 ± 0.1	0.8 ± 0.1	0.7 ± 0.1
proteins, *g/liter*	64 ± 1.1	63 ± 1.0	64 ± 1.5
creatinine, *μmoles/liter*	85 ± 6.6	79 ± 6.7	87 ± 5.9
renin activity, *ng/ml/hr*			
supine	1.12 ± 0.9	1.57 ± 0.26	2.60 ± 0.57[ad]
upright	1.72 ± 0.49	2.27 ± 0.44	5.63 ± 1.18[ad]
aldosterone, *ng/dl*			
supine	7.27 ± 0.91	6.98 ± 0.79	11.91 ± 2.93
upright	20.34 ± 6.43	28.53 ± 5.33	33.50 ± 7.99
norepinephrine, *ng/dl*			
supine	25.63 ± 7.46	29.83 ± 7.02	25.82 ± 5.21
upright	62.18 ± 13.13	61.77 ± 20.03	56.85 ± 6.71
epinephrine, *ng/dl*			
supine	2.91 ± 0.49	4.02 ± 2.03	2.40 ± 0.55
upright	8.34 ± 2.37	6.38 ± 2.46	3.55 ± 0.63
Urinary sodium, *mmoles/24 hr*	154 ± 22	158 ± 22	166 ± 20
potassium, *mmoles/24 hr*	67 ± 10	66 ± 7	61 ± 7
calcium, *mmoles/24 hr*	4.27 ± 0.50	6.53 ± 0.90	4.29 ± 0.80[d]
phosphate, *mmoles/24 hr*	25.8 ± 3.8	27.3 ± 3.7	21.4 ± 3.1
norepinephrine, *μg/g creatinine*	18.97 ± 4.70	34.27 ± 9.41	28.85 ± 7.43
epinephrine, *μg/g creatinine*	6.64 ± 2.97	8.82 ± 2.03	6.43 ± 2.31

Values are mean ± SEM.
[a] $P < 0.05$ compared with placebo.
[b] $P < 0.01$ compared with placebo.
[c] $P < 0.001$ compared with placebo.
[d] $P < 0.05$ compared with nifedipine.
[e] $P < 0.01$ compared with nifedipine.
[f] $P < 0.001$ compared with nifedipine.
[g] % of mean value relative to body surface area in 99 normal subjects [23].

acutely by these agents [13–17], but this action may dissipate within the first week [36]. When body wt was reported during short-term treatment conditions, it was, on the average, often unchanged or even slightly decreased on nifedipine or verapamil monotherapy [1, 3, 21, 37–40]. Plasma and/or blood volumes also were not significantly altered in this or previous studies [1, 3, 15, 38, 39]. No data on extracellular or total body water during calcium antagonists treatment are available. However, the sodium-blood volume constellation found in the present study may suggest that nifedipine led to an accumulation of sodium in particular outside of the extracellular space. In fact, the 1.2 kg increase in body wt during nifedipine monotherapy would suggest an increase in extracellular fluid volume of about 5%, which was matched by a 5% increase in plasma volume. However, exchangeable sodium was increased on average by 27%. The relative contribution of this excess in sodium to extracellular compartments that are relevant (vascular tissues) or irrelevant (bone, certain organs) is unknown. Moreover, the persistent antihypertensive efficacy of a calcium antagonists monotherapy in studies lasting up to 6 months [1] supports the contention that relevant body sodium-fluid volume retention, leading to progressive BP resistance, is not a prevalent characteristic of calcium antagonists, as it is of the direct arteriolar vasodilators such as the hydralazines or minoxidil.

Sodium handling by the kidneys in the established phase of nifedipine-monotherapy remains to be clarified. Activation of the sympathetic and renin-angiotensin systems could possibly constitute a sodium-retaining tendency in the early phase of treatment [1, 5, 6]. However, thereafter plasma renin and catecholamines tend to return to pre-treatment values, and their

Table 2. Norepinephrine and angiotensin II infusion in patients with essential hypertension on placebo and after nifedipine monotherapy and nifedipine-diuretic combination treatment

	Placebo	Nifedipine	Nifedipine + Chlorthalidone
Basal BP, *mm Hg*	141/92 ± 3/3	127[a]/87 ± 3/3	113[bd]/80[ce] ± 6/2
Basal heart rate, *beats/min*	69 ± 2	67 ± 2	65 ± 3
NE Infusion			
Basal plasma NE, *ng/dl*	15.6 ± 4.2	25.8 ± 4.7	30.0 ± 4.6[b]
NE pressor dose, *ng/kg/min*	113 ± 19	135 ± 29	110 ± 18
Mean slope	10.7 ± 0.8	9.3 ± 1.6	12.6 ± 1.5
Plasma NE clearance, *liter/min*	5.8 ± 1.1	5.5 ± 1.4	5.9 ± 0.8
AII Infusion			
Basal plasma AII, *pg/ml*	8.9 ± 1.0	9.4 ± 1.5	22.3 ± 4.5[ad]
Basal plasma aldosterone, *ng/dl*	4.7 ± 0.8	8.9 ± 2.0	13.8 ± 2.7[ad]
AII pressor dose, *ng/kg/min*	6.2 ± 2.0	7.9 ± 2.5	9.7 ± 3.9
Mean slope	10.4 ± 1.1	7.7 ± 2.4	9.4 ± 3.1
Plasma AII clearance, *liter/min*	5.0 ± 0.8	4.9 ± 1.1	4.2 ± 0.4

Values are mean ± SEM.
Significance levels as in Table 1.

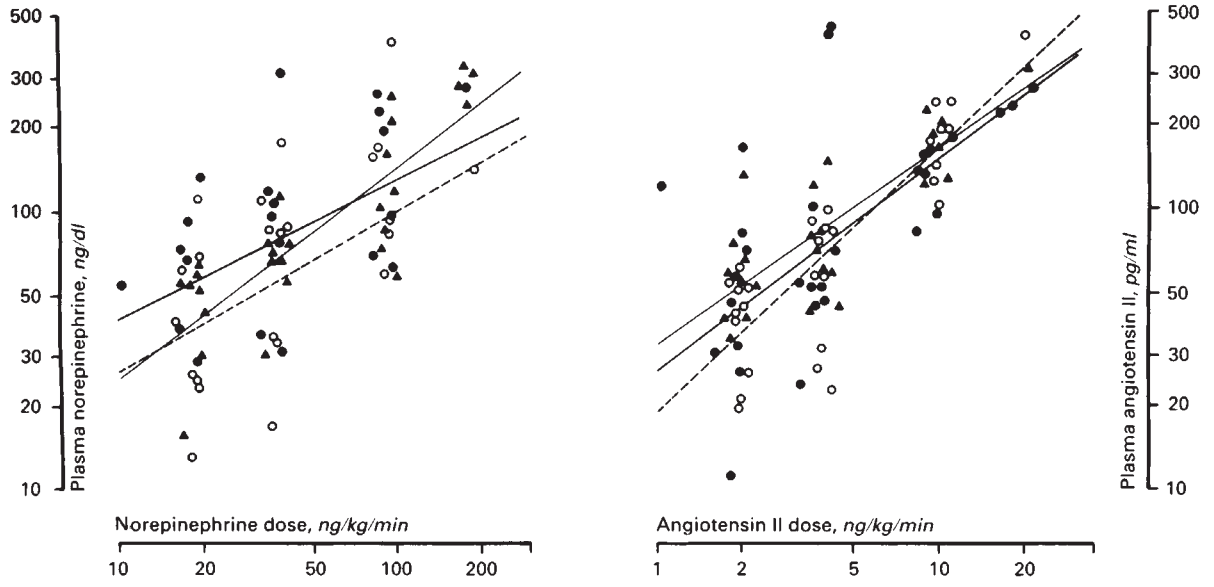

Fig. 1. *Correlations between plasma norepinephrine and norepinephrine infusion rates* (left graph) *and between plasma angiotensin II and angiotensin II infusion rates* (right graph) *in patients with essential hypertension on placebo, nifedipine monotherapy and nifedipine-diuretic treatment.* Abbreviations are: NIF, nifedipine; CHLOR, chlorthalidone. Symbols are *(left panel):* ○, placebo ($r = 0.45$, $P < 0.05$); ●, NIF ($r = 0.54$, $P < 0.01$); ▲, NIF + CHLOR ($r = 0.83$, $P = < 0.001$). *Right panel:* Symbols are the same. Correlation coefficients and probability are: $r = 0.84$, $P < 0.001$; $r = 0.58$, $P < 0.001$; $r = 0.81$, $P = < 0.001$, respectively.

unchanged levels after 6 to 8 weeks of nifedipine monotherapy in the present study are consistent with this interpretation. Plasma aldosterone levels were not increased on nifedipine therapy in this and previous investigations [1, 5, 41]. Vascular permeability may be increased [35]; this may promote a certain extravascular shift of fluid with sodium, and the resulting tendency for blood volume contraction could be compensated by a finite degree of renal sodium retention. The latter may also be favored by the setting of BP on a lower level.

Since aldosterone production in vitro requires calcium [42], the possibility of an inhibitory influence of calcium antagonists must be considered. The responsiveness of circulating aldosterone to step-wise increasing blood levels of AII was distinctly reduced ($P < 0.01$) following 6 to 8 weeks nifedipine monotherapy or nifedipine-diuretic combination treatment in our patients with mild essential hypertension, but not following 2 weeks of nifedipine monotherapy in a previously studied group of normal or borderline hypertensive subjects [7]. Others noted an immediate blunting of aldosterone response during AII infusion by nifedipine in normal subjects [43] or an acute marked lowering of plasma aldosterone by nifedipine in primary hyperaldosteronism [44]. Since nifedipine-induced vasodilation could possibly elevate liver blood flow, a partial contribution of an increased hepatic clearance to lower plasma aldosterone levels cannot be excluded [45]. Using a calcium antagonist with less vasodilating potential, namely verapamil, aldosterone stimula-

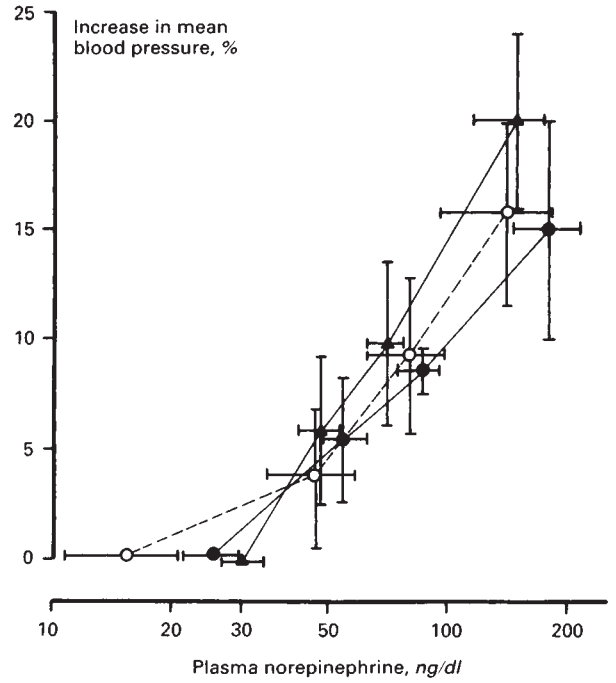

Fig. 2. *Relationship between increases in plasma norepinephrine and changes in mean blood pressure during norepinephrine infusion in patients with mild essential hypertension.* Horizontal and vertical bars represent ± SEM. Symbols are the same as Fig. 1.

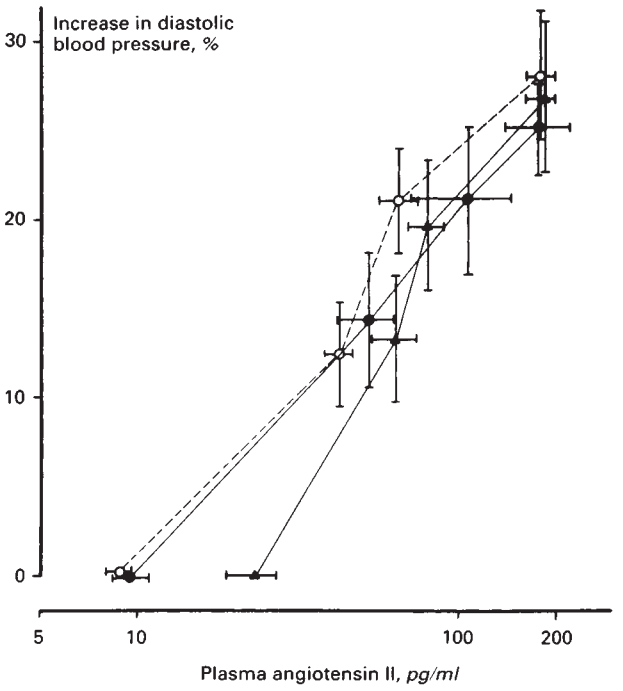

Fig. 4. *Relationship between increases in plasma angiotensin II concentrations and changes in diastolic blood pressure during angiotensin II infusion in patients with mild essential hypertension.* Horizontal and vertical bars represent ± SEM. Symbols are the same as Fig. 1.

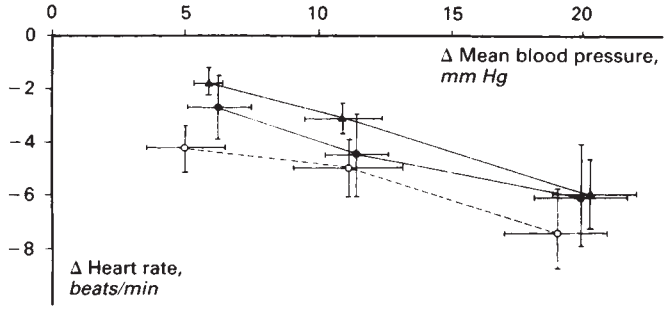

Fig. 3. *Relationship between norepinephrine-induced increases in mean blood pressure and concomitant decreases in heart rate in patients with mild essential hypertension.* Horizontal and vertical bars represent ± SEM. Symbols are the same as Fig. 1.

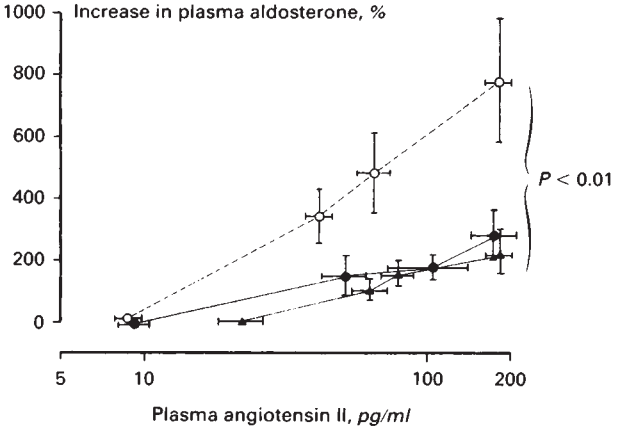

Fig. 5. *Relationship between increases in plasma angiotensin II and changes in plasma aldosterone levels during angiotensin II infusion in patients with mild essential hypertension.* Horizontal and vertical bars represent ± SEM. Symbols are the same as Fig. 1.

tion by AII in normal subjects was significantly depressed at 5 days, but not acutely after drug application [10]. The interaction between calcium antagonists and adrenal cortical function may depend on several factors, such as type and dosage of the agent, the subject's biological condition, and perhaps also the duration of pharmacological calcium antagonism. Moreover, at least nifedipine seems to interfere with aldosterone release by an AII-independent mechanism, as suggested by the potent aldosterone inhibition in a high aldosterone-low renin state [44].

Cardiovascular pressor responsiveness to NE and AII was not consistently altered following 6 to 8 weeks of nifedipine monotherapy in our hypertensive patients. The duration of pharmacological calcium antagonism could again play a role. After 4 weeks of monotherapy, pressor reactivity to NE was still lowered by nifedipine, but not by verapamil [9]. After 2 weeks of nifedipine monotherapy, NE responsiveness was decreased and AII responsiveness unaltered in normal or borderline hypertensive subjects [7]. Finally, reductions in the pressor reactivity to both NE and AII were noted following a single dose of nifedipine in normal subjects [8].

The finding, and perhaps the restoration, or largely unaltered cardiovascular pressor responses in the established phase of nifedipine monotherapy may not be surprising, since these reactions seem to be at least partly independent of extracellular calcium. Apart from transmembranous calcium influx through the slow channels, NE-induced contraction depends also on

Table 3. Basal data before calcium infusion in patients with essential hypertension on placebo and after nifedipine

	Placebo	Nifedipine
Basal BP, *mm Hg*	139/92 ± 4/3	127[a]/85 ± 3/3
Basal heart rate, *beats/min*	68 ± 3	67 ± 2
Plasma calcium, *mmoles/liter*	2.2 ± 0.1	2.2 ± 0.1
renin activity, *ng/ml/hr*	1.2 ± 0.3	1.2 ± 0.2
norepinephrine, *ng/dl*	25.3 ± 3.1	35.0 ± 9.1
epinephrine, *ng/dl*	1.8 ± 0.4	2.8 ± 0.7

Values are mean ± SEM.
Significance levels as in Table 1 and 2.

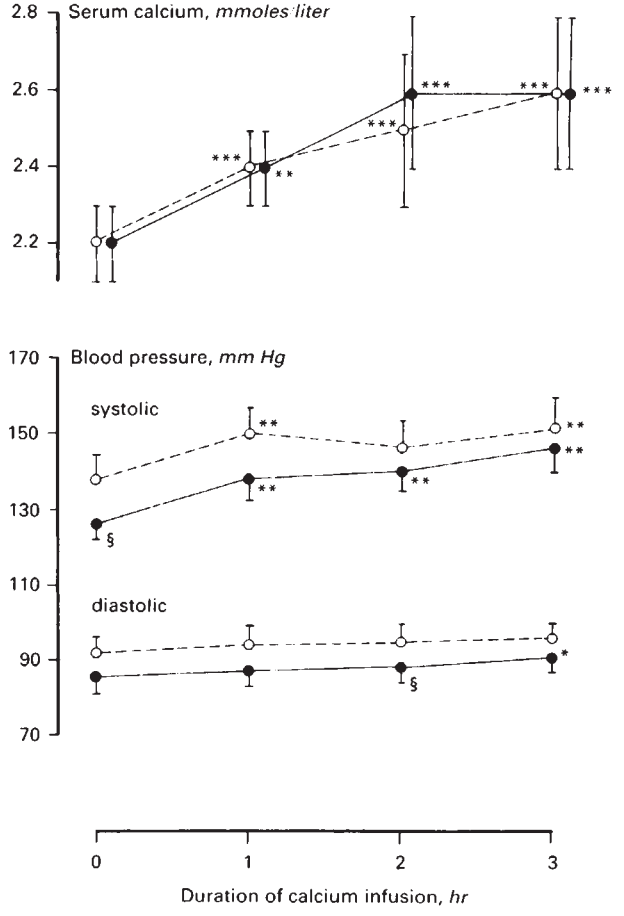

Fig. 6. *Serum calcium and blood pressure before and during intravenous calcium infusion on placebo and after nifedipine monotherapy in patients with mild essential hypertension.* Vertical bars represent ± SEM. Significance levels * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ vs. basal conditions. § $P < 0.05$ vs. placebo. Symbols are the same as Fig. 1.

calcium released from intracellular stores or binding sites [46–48], while AII-mediated contraction requires the influx of sodium [46].

Furthermore, modifications of NE reactivity could theoretically be limited to regional although important vascular beds and, therefore, not necessarily express themselves in a detectable change of overall cardiovascular pressor responsiveness. Study of this aspect is necessary to clarify whether calcium antagonists in the established phase of therapy may lower BP in essential hypertension without altering cardiovascular responsiveness to major pressor hormones.

The increase in systolic and, to a lesser extent, diastolic BP accompanying mild hypercalcemia [18, 19] was not inhibited by nifedipine in our patients. This suggests that pressor responses during acute hypercalcemia are not mediated by an enhanced influx of calcium through the slow transmembranous channels. The preferential influence on systolic BP may possibly suggest a decreased compliance and diameter of large arteries as a pathogenetic component. One investigator has even proposed that a factor other than hypercalcemia per se may be responsible for the rise in BP in this setting [49]. Whatever the exact mechanisms of hypercalcemia-associated acute hypertension, our observations suggest that a calcium infusion remains a potential BP-elevating maneuver even in the presence of pharmacological calcium antagonism. Intravenous calcium has already been found to improve unwanted cardiodepression induced by certain calcium antagonists [50].

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